

Appl. No. 10/781,062

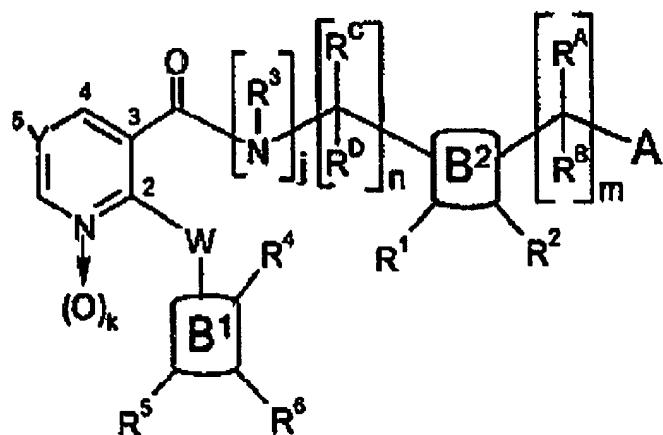
Amendment dated June 9, 2006

Reply to Office Action of March 9, 2006

Listing of Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

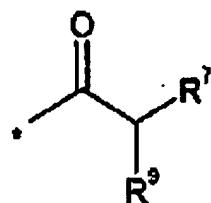
1. (currently amended) A compound of Formula (1.0.0):



(1.0.0)

— wherein —

- j is 0 or 1; provided that when j is 0, n must be 2;
- k is 0 or 1;
- m is 0, 1, or 2;
- n is 1 or 2;
- A is



(1.1.3)

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— wherein —

—^{“*”} indicates the point of attachment of each partial Formula (1.1.3) (1.1.1) through (1.1.5) to the remaining portion of Formula (1.0.0);

--R⁷ is a member independently selected from the group consisting of
— the following: —

—(1) -H;

—(2) -(C₁-C₆) alkyl; -(C₂-C₆) alkenyl; or -(C₂-C₆) alkynyl; where said alkyl, alkenyl or alkynyl is substituted by 0 to 3 substituents R¹⁰;

— where —

---R¹⁰ is a member selected from the group consisting of phenyl; pyridyl; -F; -Cl; -CF₃; oxo (=O); -OR¹⁶; -NO₂; -CN; -C(=O)OR¹⁶; -O-C(=O)R¹⁶; -C(=O)NR¹⁶R¹⁷; -O-C(=O)NR¹⁶R¹⁷; -NR¹⁶R¹⁷; -NR¹⁶C(=O)R¹⁷; -NR¹⁶C(=O)OR¹⁷; -NR¹⁶S(=O)₂R¹⁷; and -S(=O)₂NR¹⁶R¹⁷; where said phenyl or pyridyl is substituted by 0 to 3 R¹²;

— where —

----R¹² is -F; -Cl; -CF₃; -CN; -NO₂; -OH; -(C₁-C₃) alkoxy; -(C₁-C₃) alkyl; or -NR¹⁶R¹⁷;

— and —

---R¹⁶ and R¹⁷ are each a member independently selected from the group consisting of -H; -(C₁-C₄) alkyl; -(C₂-C₄) alkenyl; -(C₃-C₆) cycloalkyl; phenyl; benzyl; and pyridyl; wherein said alkyl, alkenyl, cycloalkyl, phenyl, benzyl, or pyridyl is substituted by 0 to 3 substituents selected from the group consisting of -F, -Cl, -CF₃, -CN, and -(C₁-C₃) alkyl;

--(3) -(CH₂)_u-(C₃-C₇) cycloalkyl where u is 0, 1 or 2; and further where said (C₃-C₇) cycloalkyl is substituted by 0 to 3 substituents R¹⁰ where R¹⁰ has the same meaning as defined above;

— and —

--(4) phenyl or benzyl, where said phenyl or benzyl is independently substituted by 0 to 3 substituents R¹⁰ where R¹⁰ has the same meaning as defined above;

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R¹⁸ is selected from the group consisting of -H; -(C₁-C₄) alkyl; and phenyl;
-R⁹ is a member selected from the group consisting of -H; -(C₁-C₄) alkyl; -(C₃-C₇) cycloalkyl; phenyl; benzyl; pyridyl; -C(=O)OR¹⁸; -C(=O)R¹⁸; -OR¹⁸; -(C₁-C₂) alkyl-OR¹⁸; and -(C₁-C₂) alkyl-C(=O)OR¹⁸; where R¹⁸ has the same meaning as defined above; however, when m is 0, and R⁷ is C₁ alkyl, then R⁹ is not H, and when m is 0, and R⁹ is C₁ alkyl, then R⁷ is not H;

-W is -O-; -S(=O)_t, where t is 0, 1, or 2; or -N(R³)- where R³ has the same meaning as defined below;

-Y is =C(R^{1a})-, where R^{1a} has the same meaning as defined below; or

~~-[N-(O)_k]~~ where k is 0 or 1;

- where -

--R^{1a} is a member selected from the group consisting of -H; -F; -Cl; -CN; -NO₂; -(C₁-C₄) alkyl; -(C₂-C₄) alkynyl; fluorinated-(C₁-C₃) alkyl; fluorinated-(C₁-C₃) alkoxy; -OR¹⁶; and -C(=O)NR^{12a}R^{12b};

- where -

--R^{12a} and R^{12b} are each independently -H; -CH₃; -CH₂CH₃; -CH₂CH₂CH₃; -CH₂(CH₃)₂; -CH₂CH₂CH₂CH₃; -CH(CH₃)CH₂CH₃; -CH₂CH(CH₃)₂; -C(CH₃)₃; cyclopropyl; cyclobutyl; or cyclopentyl;

-R^A and R^B are each a member independently selected from the group consisting of -H; -F; -CF₃; -(C₁-C₄) alkyl; -(C₃-C₇) cycloalkyl; phenyl; and benzyl; wherein said cycloalkyl, phenyl, and benzyl moieties are each independently substituted with 0 to 3 substituents R¹⁰ where R¹⁰ has the same meaning as defined above;

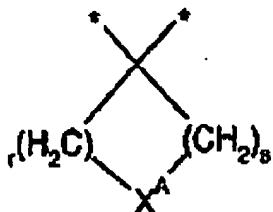
- or -

-R^A and R^B are taken together, but only in the case where m is 1, to form a spiro moiety of Formula (1.2.0):

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(1.2.0)

- where -

-r and s are independently 0 to 4 provided that the sum of r + s is at least 1 but not greater than 5;

- and -

-X^A is -CH₂-, -CHR¹²-, or -C(R¹²)₂- where each R¹² is selected independently of the other and each has the same meaning as defined above; -NR¹⁵-, where R¹⁵ has the same meaning as defined above; -O-; or -S(=O)_t, where t is 0, 1, or 2; and said spiro moiety is substituted as to any one or more carbon atoms thereof by 0 to 3 substituents R¹⁴, as to a nitrogen atom thereof by 0 or 1 substituent R¹⁵, and as to a sulfur atom thereof by 0 or 2 oxygen atoms;

-R^C and R^D have the same meaning as defined above for R^A and R^B except that one of them must be -H, and they are selected independently of each other and of R^A and R^B;

-R¹ and R² may individually or together appear on any ring or rings comprising a meaning of the moiety B² as defined below, and R¹ and R² are each a member independently selected from the group consisting of -H; -F; -Cl; -CN; -NO₂; -(C₁-C₄) alkyl; -(C₂-C₄) alkynyl; fluorinated-(C₁-C₃) alkyl; -OR¹⁶; and -C(=O)NR^{12a}R^{12b}; where R^{12a} and R^{12b} have the same meanings as defined above;

-R³ is -H; -(C₁-C₃) alkyl; phenyl; benzyl; or -OR¹⁶, where R¹⁶ has the same meaning as defined above;

-R⁴, R⁵ and R⁶ may individually or together appear on any ring or rings comprising a meaning of the moiety B¹ as defined below, and R⁴, R⁵ and R⁶ are each a member independently selected from the group consisting of

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— the following: —

-(a) -H; provided that R⁵ and R⁶ are not both -H at the same time; -F; -Cl; -(C₂-C₄) alkynyl; -R¹⁶; -OR¹⁶; -S(=O)_pR¹⁶; -C(=O)R¹⁶; -C(=O)OR¹⁶; -OC(=O)R¹⁶; -CN; -NO₂; -C(=O)NR¹⁶R¹⁷; -OC(=O)NR¹⁶R¹⁷; -NR¹²_aC(=O)NR¹⁶R¹⁷; -NR¹²_aC(=NR¹²)NR¹⁶R¹⁷; -NR¹²_aC(=NCN)NR¹⁶R¹⁷; -NR¹²_aC(=N-NO₂)NR¹⁶R¹⁷; -C(=NR¹²_a)NR¹⁶R¹⁷; -CH₂C(=NR¹²_a)NR¹⁶R¹⁷; -OC(=NR¹²_a)NR¹⁶R¹⁷; -OC(=N-NO₂)NR¹⁶R¹⁷; -NR¹⁶R¹⁷; -CH₂NR¹⁶R¹⁷; -NR¹²_aC(=O)R¹⁶; -NR¹²_aC(=O)OR¹⁶; =NOR¹⁶; -NR¹²_aS(=O)_pR¹⁷; -S(=O)_pNR¹⁶R¹⁷; and -CH₂C(=NR¹²_a)NR¹⁶R¹⁷;

— where —

-p is 0, 1, or 2; and R¹²_a, R¹⁶, and R¹⁷ have the same meanings as defined above;

-(b) -(C₁-C₄) alkyl; and -(C₁-C₄) alkoxy, where R⁴, R⁵, or R⁶ has the meaning of -OR¹⁶ under (A) above and R¹⁶ is defined as -(C₁-C₄) alkyl; wherein said alkyl and alkoxy are each independently substituted with 0 to 3 substituents -F or -Cl; or 0 or 1 substituent (C₁-C₂) alkoxy carbonyl-; (C₁-C₂) alkyl carbonyl-; or (C₁-C₂) alkyl carbonyloxy-;

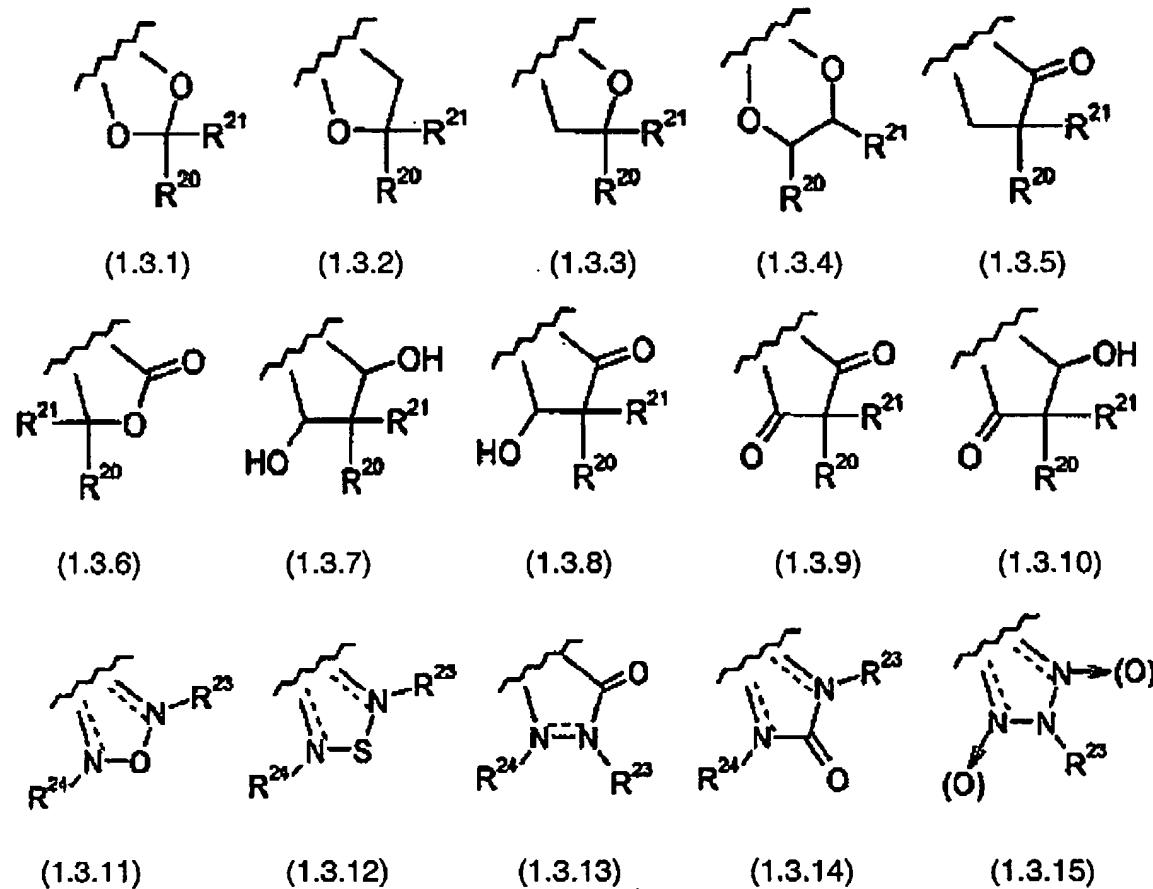
— and —

-(c) an aryl or heterocyclyl moiety selected from the group consisting of phenyl; benzyl; furanyl; tetrahydrofuran; oxetanyl; thienyl; tetrahydrothienyl; pyrrolyl; pyrrolidinyl; oxazolyl; oxazolidinyl; isoxazolyl; isoxazolidinyl; thiazolyl; thiazolidinyl; isothiazolyl; isothiazolidinyl; pyrazolyl; pyrazolidinyl; oxadiazolyl; thiadiazolyl; imidazolyl; imidazolidinyl; pyridinyl; pyrazinyl; pyrimidinyl; pyridazinyl; piperidinyl; piperazinyl; triazolyl; triazinyl; tetrazolyl; pyranyl; azetidinyl; morpholinyl; parathiazinyl; indolyl; indolinyl; benzo[b]furanyl; 2,3-dihydrobenzofuranyl; 2-H-chromenyl; chromanyl; benzothienyl; 1-H-indazolyl; benzimidazolyl; benzoxazolyl; benzisoxazolyl; benzthiazolyl; quinolinyl; isoquinolinyl; phthalazinyl; quinazolinyl; quinoxalinyl; and purinyl; wherein said aryl and heterocyclyl moieties are each independently substituted with 0 to 2 substituents R¹⁴ where R¹⁴ has the same meaning as defined above;

— or in the case where B¹ is phenyl —

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-(d) R^5 and R^6 are taken together to form a moiety which is a member selected from the group consisting of partial Formulas (1.3.1) through (1.3.15):



– wherein –

$-R^{20}$ and R^{21} are each a member independently selected from the group consisting of -H; -F; -Cl; -CH₃; -CH₂F; -CHF₂; -CF₃; -OCH₃; and -OCF₃;
 $-R^{23}$ and R^{24} are each independently -H; -CH₃; -OCH₃; -CH₂CH₃; -OCH₂CH₃; -CH₂CH₂CH₃; -CH₂(CH₃)₂; -CH₂CH₂CH₂CH₃; -CH(CH₃)CH₂CH₃; -CH₂CH(CH₃)₂; -C(CH₃)₃; or absent, in which case the dashed line - - - represents a double bond, provided that in partial Formula (1.3.11) R^{23} and R^{24} may not both be absent at the same time;

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-B¹ is a moiety comprising a saturated or unsaturated carbon ring system that is 3- to 7-membered monocyclic, or that is 7- to 12-membered, fused or discontinuous, polycyclic; wherein ~~optionally one carbon atom thereof may be replaced by a heteroatom selected from N, O, and S; and where N is selected, optionally a second carbon atom thereof may be replaced by a heteroatom selected from N, O, or S;~~

- wherein -

said moiety defining B¹ is substituted on any ring or rings thereof by R⁴, R⁵ and R⁶, which have the same meaning as defined above;

-B² is a moiety comprising a saturated or unsaturated carbon ring system that is 3- to 7-membered monocyclic, or that is 7- to 12-membered, fused or discontinuous, polycyclic; wherein ~~optionally one carbon atom thereof may be replaced by a heteroatom selected from N, O, and S; and where N is selected, optionally a second carbon atom thereof may be replaced by a heteroatom selected from N, O, or S;~~

- wherein -

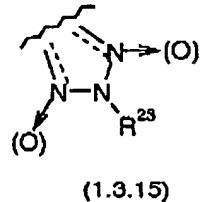
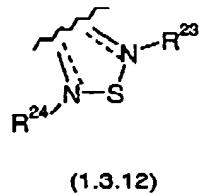
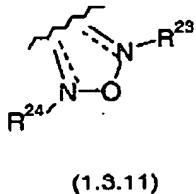
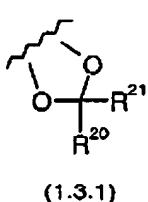
said moiety defining B² is substituted on any ring or rings thereof by R¹ and R², which have the same meaning as defined above;

- or -

a pharmaceutically acceptable salt thereof.

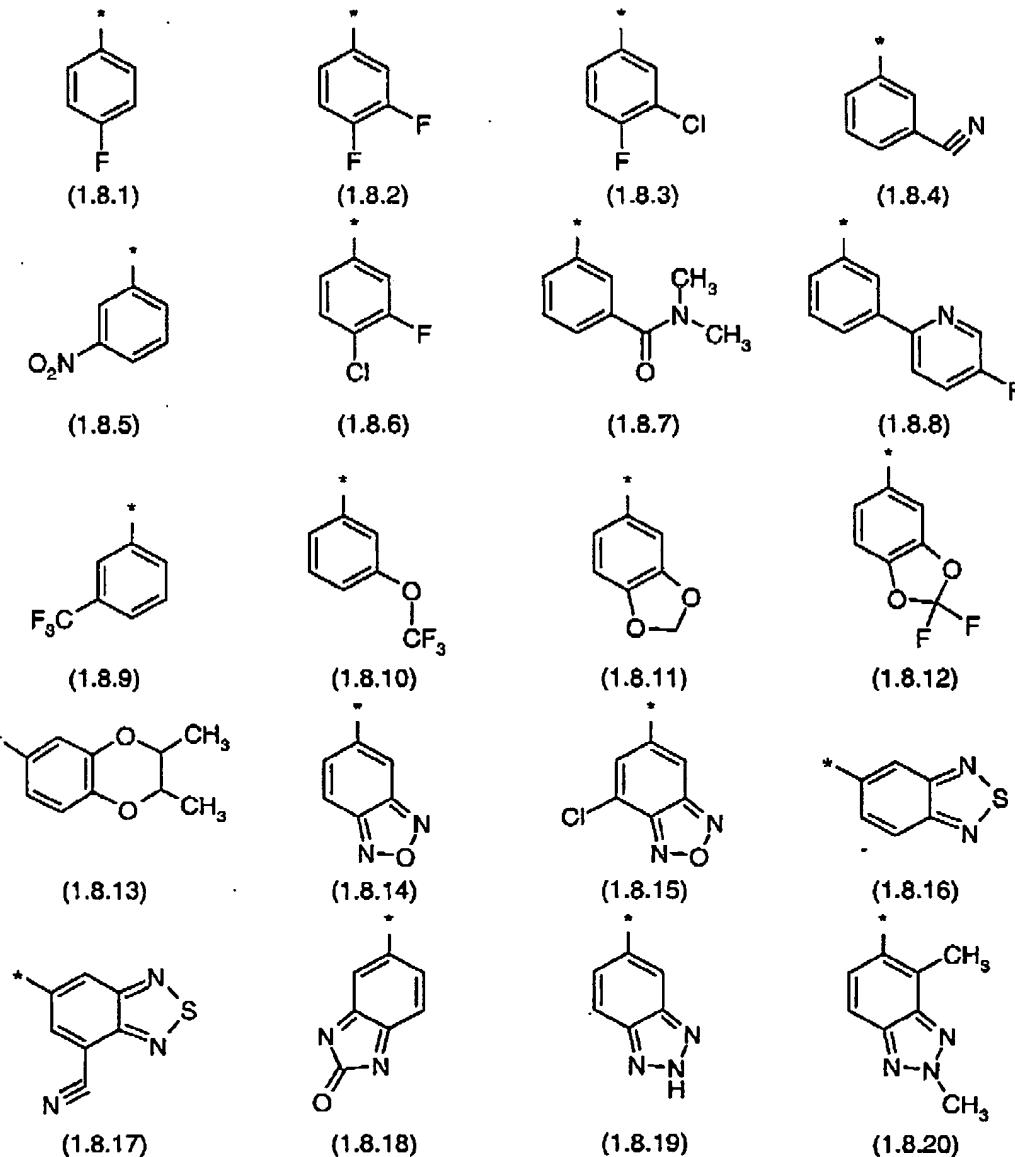
2.-7. (cancelled).

8. (original) A compound according to Claim 1 wherein the moiety B¹ is phenyl and R⁵ and R⁶ are taken together to form a moiety which is a member selected from the group consisting of partial Formulas (1.3.1), (1.3.11), (1.3.12), and (1.3.15):

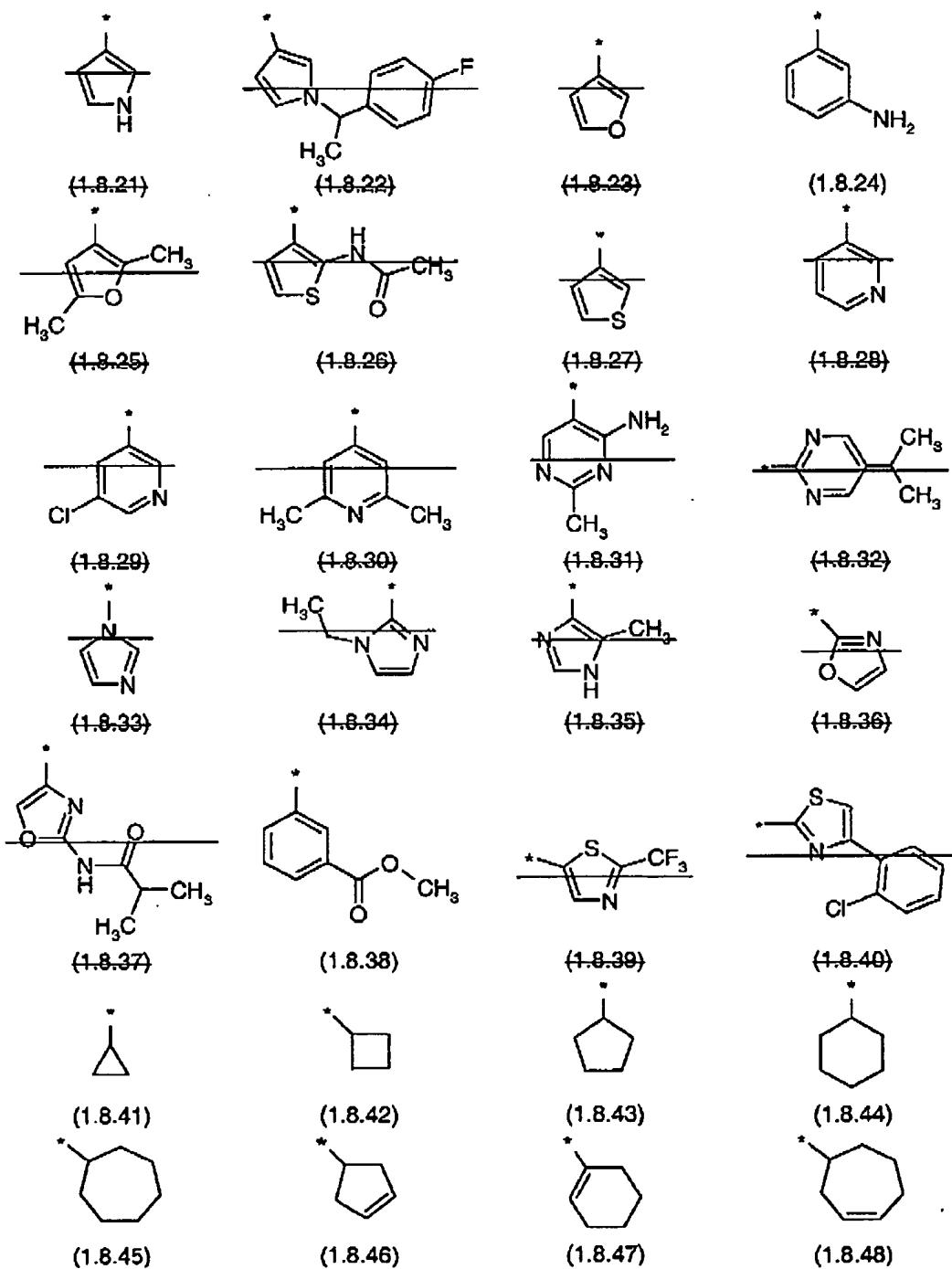


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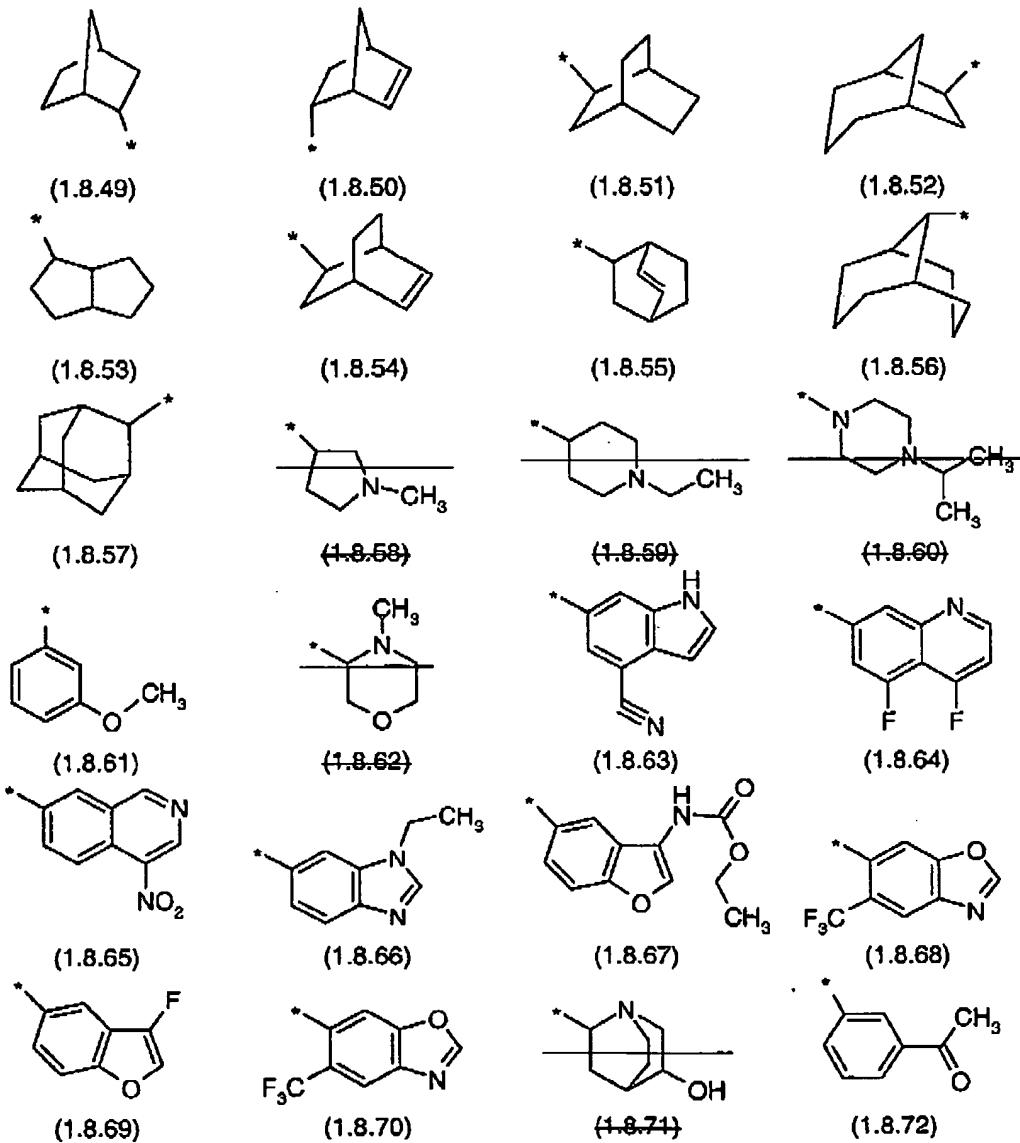
9. (currently amended) A compound according to Claim 1 wherein B¹ and the substituents R⁴, R⁵, and R⁶ are selected in such a way that the left-hand terminus of said compound of Formula (1.0.0) is represented by the following partial Formulas (1.8.1) through (1.8.72):



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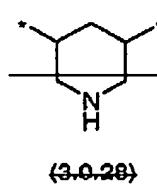
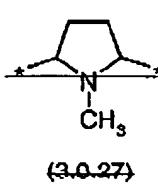
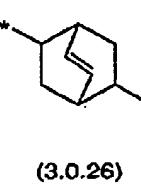
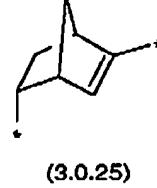
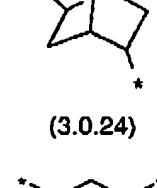
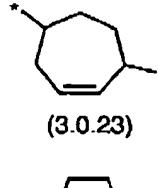
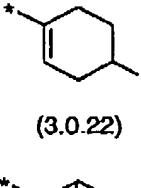
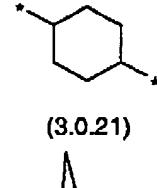
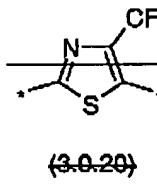
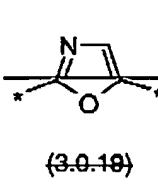
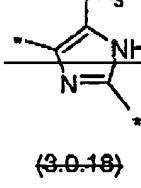
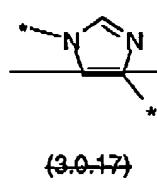
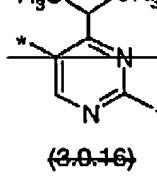
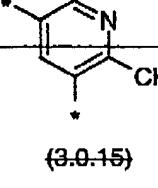
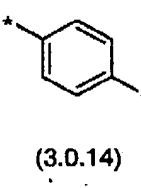
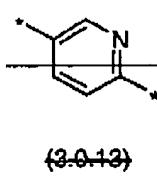
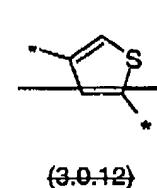
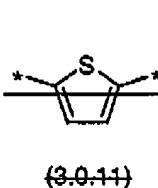
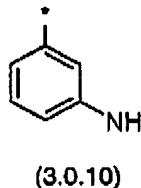
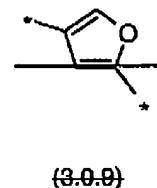
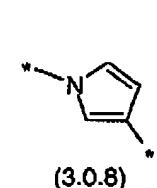
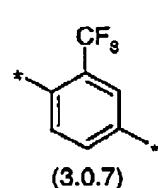
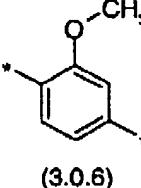
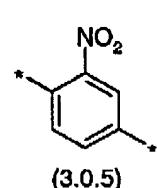
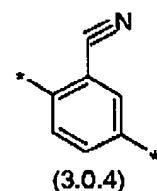
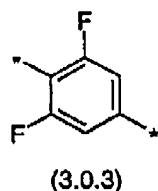
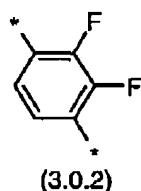
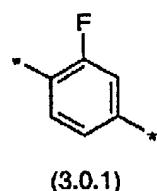


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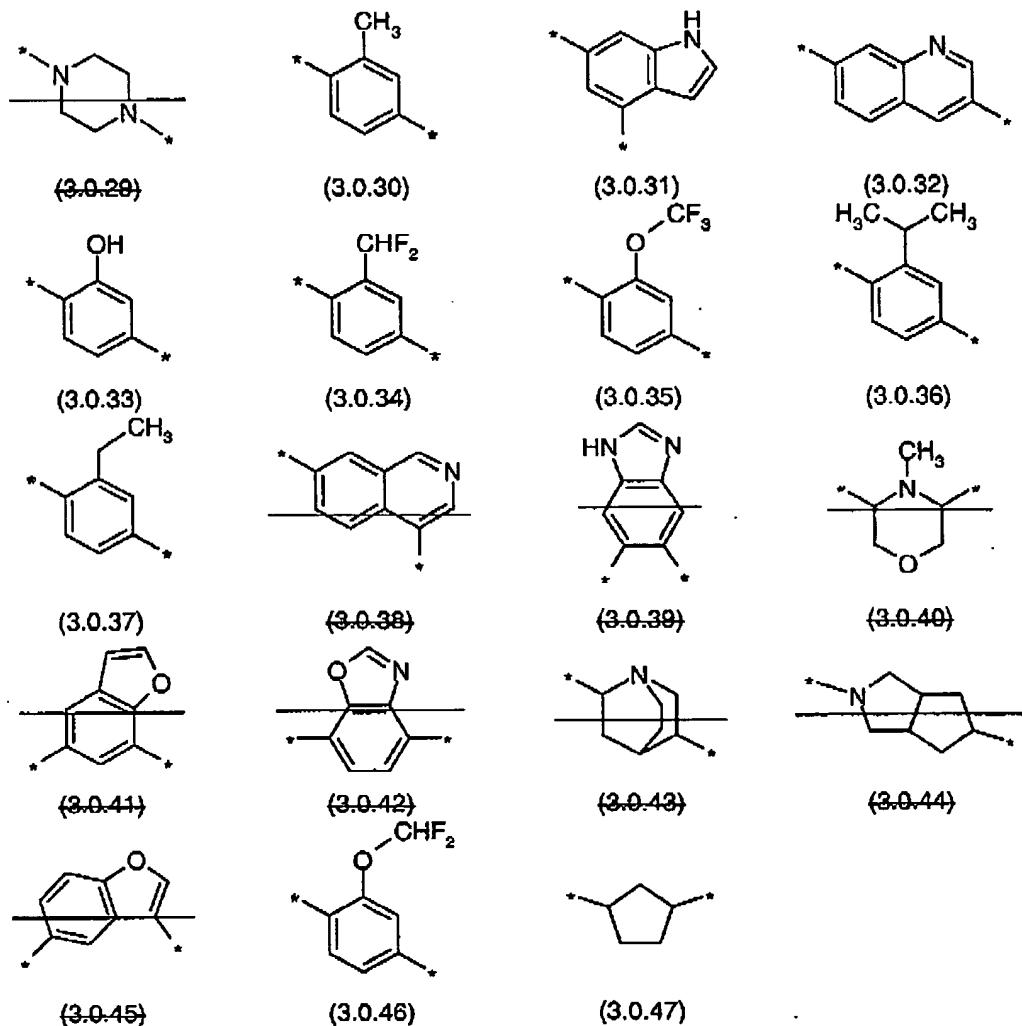


10. (currently amended) A compound according to Claim 1 wherein B² and the substituents R¹ and R² are selected in such a way that this portion of the right-hand terminus of said compound of Formula (1.0.0) is represented by the following partial Formulas (3.0.1) through (3.0.47):

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11.-12. (cancelled).

13. (currently amended) A compound according to Claim 1 wherein B^1 and B^2 are independently phenyl or pyridyl; m is 1; n is 1; A is a moiety of partial Formula (1.1.3) where R^7 is -H, or -CH₃ or phenyl independently substituted by 0 or 1 R^{10} where R^{10} is pyridyl or phenyl substituted by 0-2 of -F, -Cl, -OCH₃, -CN, -NO₂, or -NR¹⁶R¹⁷ where R¹⁶ and R¹⁷ are -H or -CH₃; or R^{10} is -F, -Cl, -CF₃, -CN, -OCH₃, -NO₂, -C(=O)OR¹⁶, NR¹⁶R¹⁷,

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or $-S(=O)_2NR^{16}R^{17}$ where R^{16} and R^{17} are -H or $-CH_3$; R^9 is -H or $-CH_3$; W is -O-; Y is $=C(R^{18})-$; R^{18} is -H; or -F; R^A and R^B are independently -H or $-CH_3$; or R^A and R^B are taken together to form a $-(C_3-C_7)$ cycloalkyl-spiro moiety; one of R^C and R^D is -H and the other is -H or $-CH_3$; R^1 and R^2 are -H, -F, or $-OCH_3$; R^3 is -H or $-CH_3$; and R^4 , R^5 and R^6 are -H provided that R^5 and R^6 are not both -H at the same time, -F, -Cl, $-OCH_3$, -CN; $-NO_2$, or $-C(=O)R^3$ or $-C(=O)OR^3$ where R^3 is $-CH_3$; or R^5 and R^6 are taken together to form a moiety of partial Formula (1.3.1), (1.3.2), (1.3.3), (1.3.11), (1.3.12), or (1.3.15), where for partial Formulas (1.3.11), (1.3.12), and (1.3.15), R^{23} and R^{24} are both absent.

14. (original) A compound according to Claim 13 wherein R^7 is -H; R^9 is -H; R^A and R^B are taken together to form a cyclopropyl-spiro or cyclobutyl-spiro moiety; R^C and R^D are both -H; R^3 is -H; R^4 and R^5 are both -H, and R^6 is -F; or R^5 and R^6 are taken together to form a moiety of partial Formula (1.3.1) or (1.3.11).

15.-16. (cancelled).

17. (currently amended) A compound according to Claim 1 wherein said compound is a member selected from the group consisting of the following:

2-(Benzo[1,3]dioxol-5-yloxy)-N-[4-(1-carbamoyl-1-methyl-ethyl)-benzyl]-nicotinamide of Formula;

2-(Benzo[1,3]dioxol-5-yloxy)-N-(4-carbamoylmethyl-benzyl)-nicotinamide;

N-(4-Carbamoylmethyl-2-fluoro-benzyl)-2-(4-fluoro-phenoxy)-nicotinamide;

2-(Benzo[1,3]dioxol-5-yloxy)-N-[4-(1-carbamoyl-1-methyl-ethyl)-2-fluoro-benzyl]-nicotinamide;

N-[4-(1-Carbamoyl-1-methyl-ethyl)-2-fluoro-benzyl]-2-(4-fluoro-phenoxy)-nicotinamide;

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2-(Benzo[1,3]dioxol-5-yloxy)-N-[4-(1-methyl-1-methylcarbamoyl-ethyl)-benzyl]-nicotin-amide;

2-(Benzo[1,3]dioxol-5-yloxy)-N-{4-[1-(cyclopropylmethyl-carbamoyl)-1-methyl-ethyl]-benzyl}-nicotinamide; or

2-(Benzo[1,3]dioxol-5-yloxy)-N-[4-(1-ethylcarbamoyl-1-methyl-ethyl)-benzyl]-nicotin-amide.

18. (Original) A method of treating a subject suffering from a disease, disorder or condition mediated by the PDE4 isozyme whereby it regulates the activation and degranulation of eosinophils, comprising administering to said subject in need of said treatment a therapeutically effective amount of a compound of Formula (1.0.0).

19. (Original) A pharmaceutical composition for use in treating a subject suffering from a disease, disorder or condition mediated by the PDE4 isozyme whereby it regulates the activation and degranulation of eosinophils, comprising a therapeutically effective amount of a compound of Formula (1.0.0) as defined in Claim 1 together with a pharmaceutically acceptable carrier therefor.

20. (original) A method according to Claim 18 wherein said disease, disorder, or condition comprises one or more members selected from the group consisting of:

— asthma of whatever type, etiology, or pathogenesis; or asthma that is a member selected from the group consisting of atopic asthma; non-atopic asthma; allergic asthma; atopic, bronchial, IgE-mediated asthma; bronchial asthma; essential asthma; true asthma; intrinsic asthma caused by pathophysiologic disturbances; extrinsic asthma caused by environmental factors; essential asthma of unknown or inapparent cause; non-atopic asthma; bronchitic asthma; emphysematous asthma; exercise-induced asthma; occupational asthma; infective asthma caused by bacterial,

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fungal, protozoal, or viral infection; non-allergic asthma; incipient asthma; wheezy infant syndrome;

— chronic or acute bronchoconstriction; chronic bronchitis; small airways obstruction; and emphysema;

— obstructive or inflammatory airways diseases of whatever type, etiology, or pathogenesis; or an obstructive or inflammatory airways disease that is a member selected from the group consisting of asthma; pneumoconiosis; chronic eosinophilic pneumonia; chronic obstructive pulmonary disease (COPD); COPD that includes chronic bronchitis, pulmonary emphysema or dyspnea associated therewith; COPD that is characterized by irreversible, progressive airways obstruction; adult respiratory distress syndrome (ARDS), and exacerbation of airways hyper-reactivity consequent to other drug therapy;

— pneumoconiosis of whatever type, etiology, or pathogenesis; or pneumoconiosis that is a member selected from the group consisting of aluminosis or bauxite workers' disease; anthracosis or miners' asthma; asbestosis or steam-fitters' asthma; chalcosis or flint disease; ptosis caused by inhaling the dust from ostrich feathers; siderosis caused by the inhalation of iron particles; silicosis or grinders' disease; byssinosis or cotton-dust asthma; and talc pneumoconiosis;

— bronchitis of whatever type, etiology, or pathogenesis; or bronchitis that is a member selected from the group consisting of acute bronchitis; acute laryngotracheal bronchitis; arachidic bronchitis; catarrhal bronchitis; croupous bronchitis; dry bronchitis; infectious asthmatic bronchitis; productive bronchitis; staphylococcus or streptococcal bronchitis; and vesicular bronchitis;

— bronchiectasis of whatever type, etiology, or pathogenesis; or bronchiectasis that is a member selected from the group consisting of cylindric bronchiectasis; sacculated bronchiectasis; fusiform bronchiectasis; capillary bronchiectasis; cystic bronchiectasis; dry bronchiectasis; and follicular bronchiectasis;

— seasonal allergic rhinitis; or perennial allergic rhinitis; or sinusitis of whatever type, etiology, or pathogenesis; or sinusitis that is a member selected from the group

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consisting of purulent or nonpurulent sinusitis; acute or chronic sinusitis; and ethmoid, frontal, maxillary, or sphenoid sinusitis;

— rheumatoid arthritis of whatever type, etiology, or pathogenesis; or rheumatoid arthritis that is a member selected from the group consisting of acute arthritis; acute gouty arthritis; chronic inflammatory arthritis; degenerative arthritis; infectious arthritis; Lyme arthritis; proliferative arthritis; psoriatic arthritis; and vertebral arthritis;

— gout, and fever and pain associated with inflammation;

— an eosinophil-related disorder of whatever type, etiology, or pathogenesis; or an eosinophil-related disorder that is a member selected from the group consisting of eosinophilia; pulmonary infiltration eosinophilia; Loffler's syndrome; chronic eosinophilic pneumonia; tropical pulmonary eosinophilia; bronchopneumonic aspergillosis; aspergilloma; granulomas containing eosinophils; allergic granulomatous angiitis or Churg-Strauss syndrome; polyarteritis nodosa (PAN); and systemic necrotizing vasculitis;

— atopic dermatitis; or allergic dermatitis; or allergic or atopic eczema;

— urticaria of whatever type, etiology, or pathogenesis; or urticaria that is a member selected from the group consisting of immune-mediated urticaria; complement-mediated urticaria; urticariogenic material-induced urticaria; physical agent-induced urticaria; stress-induced urticaria; idiopathic urticaria; acute urticaria; chronic urticaria; angioedema; cholinergic urticaria; cold urticaria in the autosomal dominant form or in the acquired form; contact urticaria; giant urticaria; and papular urticaria;

— conjunctivitis of whatever type, etiology, or pathogenesis; or conjunctivitis that is a member selected from the group consisting of actinic conjunctivitis; acute catarrhal conjunctivitis; acute contagious conjunctivitis; allergic conjunctivitis; atopic conjunctivitis; chronic catarrhal conjunctivitis; purulent conjunctivitis; and vernal conjunctivitis;

— uveitis of whatever type, etiology, or pathogenesis; or uveitis that is a member selected from the group consisting of inflammation of all or part of the uvea; anterior uveitis; iritis; cyclitis; iridocyclitis; granulomatous uveitis; nongranulomatous uveitis; phacoantigenic uveitis; posterior uveitis; choroiditis; and chorioretinitis;

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- psoriasis;
- multiple sclerosis of whatever type, etiology, or pathogenesis; or multiple sclerosis that is a member selected from the group consisting of primary progressive multiple sclerosis; and relapsing remitting multiple sclerosis;
- autoimmune/inflammatory diseases of whatever type, etiology, or pathogenesis; or an autoimmune/inflammatory disease that is a member selected from the group consisting of autoimmune hematological disorders; hemolytic anemia; aplastic anemia; pure red cell anemia; idiopathic thrombocytopenic purpura; systemic lupus erythematosus; polychondritis; scleroderma; Wegner's granulomatosis; dermatomyositis; chronic active hepatitis; myasthenia gravis; Stevens-Johnson syndrome; idiopathic sprue; autoimmune inflammatory bowel diseases; ulcerative colitis; Crohn's disease; endocrin ophthamopathy; Grave's disease; sarcoidosis; alveolitis; chronic hypersensitivity pneumonitis; primary biliary cirrhosis; juvenile diabetes or diabetes mellitus type I; anterior uveitis; granulomatous or posterior uveitis; keratoconjunctivitis sicca; epidemic keratoconjunctivitis; diffuse interstitial pulmonary fibrosis or interstitial lung fibrosis; idiopathic pulmonary fibrosis; cystic fibrosis; psoriatic arthritis; glomerulonephritis with and without nephrotic syndrome; acute glomerulonephritis; idiopathic nephrotic syndrome; minimal change nephropathy; inflammatory/hyperproliferative skin diseases; psoriasis; atopic dermatitis; contact dermatitis; allergic contact dermatitis; benign familial pemphigus; pemphigus erythematosus; pemphigus foliaceus; and pemphigus vulgaris;
- prevention of allogeneic graft rejection following organ transplantation;
- inflammatory bowel disease (IBD) of whatever type, etiology, or pathogenesis; or inflammatory bowel disease that is a member selected from the group consisting of ulcerative colitis (UC); collagenous colitis; colitis polyposa; transmural colitis; and Crohn's disease (CD);
- septic shock of whatever type, etiology, or pathogenesis; or septic shock that is a member selected from the group consisting of renal failure; acute renal failure; cachexia; malarial cachexia; hypophysial cachexia; uremic cachexia; cardiac cachexia;

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cachexia suprarenalis or Addison's disease; cancerous cachexia; and cachexia as a consequence of infection by the human immunodeficiency virus (HIV);

- liver injury;
- pulmonary hypertension; and hypoxia-induced pulmonary hypertension;
- bone loss diseases; primary osteoporosis; and secondary osteoporosis;
- central nervous system disorders of whatever type, etiology, or pathogenesis; or a central nervous system disorder that is a member selected from the group consisting of depression; Parkinson's disease; learning and memory impairment; tardive dyskinesia; drug dependence; arteriosclerotic dementia; and dementias that accompany Huntington's chorea, Wilson's disease, paralysis agitans, and thalamic atrophies;
- infection, especially infection by viruses wherein such viruses increase the production of TNF- α in their host, or wherein such viruses are sensitive to upregulation of TNF- α in their host so that their replication or other vital activities are adversely impacted, including a virus which is a member selected from the group consisting of HIV-1, HIV-2, and HIV-3; cytomegalovirus, CMV; influenza; adenoviruses; and Herpes viruses, including *Herpes zoster* and *Herpes simplex*;
- yeast and fungus infections wherein said yeast and fungi are sensitive to upregulation by TNF- α or elicit TNF- α production in their host, when administered in conjunction with other drugs of choice for the treatment of systemic yeast and fungus infections, including but not limited to, polymixins, Polymycin B; imidazoles, clotrimazole, econazole, miconazole, and ketoconazole; triazoles, fluconazole and itraconazole; and amphotericins, Amphotericin B and liposomal Amphotericin B; and
- ischemia-reperfusion injury; autoimmune diabetes; retinal autoimmunity; chronic lymphocytic leukemia; HIV infections; lupus erythematosus; kidney and ureter disease; urogenital and gastrointestinal disorders; and prostate diseases.

21. (currently amended) A method of treatment according to Claim 20 wherein said disease, disorder, or condition is a member selected from the group consisting consisting of (1) inflammatory diseases and conditions comprising: joint inflammation,

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rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, inflammatory bowel disease, ulcerative colitis, chronic glomerulonephritis, dermatitis, and Crohn's disease; (2) respiratory diseases and conditions comprising: asthma, acute respiratory distress syndrome, chronic pulmonary inflammatory disease, bronchitis, chronic obstructive airway disease, and silicosis; (3) infectious diseases and conditions comprising: sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, fever and myalgias due to bacterial, viral or fungal infection, and influenza; (4) immune diseases and conditions comprising: autoimmune diabetes, systemic lupus erythematosus, graft vs. host reaction, allograft rejections, multiple sclerosis, psoriasis, and allergic rhinitis; and (5) other diseases and conditions comprising: bone resorption diseases; reperfusion injury; cachexia secondary to infection or malignancy; cachexia secondary to human acquired immune deficiency syndrome (AIDS), human immunodeficiency virus (HIV) infection, or AIDS related complex (ARC); keloid formation; scar tissue formation; type 1 diabetes mellitus; and leukemia.

22. (original) The combination of a compound of Formula (1.0.0) as defined in Claim 1 together with one or more members selected from the group consisting of the following:

- (a) Leukotriene biosynthesis inhibitors, 5-lipoxygenase (5-LO) inhibitors, and 5-lipoxygenase activating protein (FLAP) antagonists selected from the group consisting of zileuton; ABT-761; fenleuton; tepoxalin; Abbott-79175; Abbott-85761; *N*-(5-substituted)-thiophene-2-alkylsulfonamides of Formula (5.2.8); 2,6-di-*tert*-butylphenol hydrazones of Formula (5.2.10); Zeneca ZD-2138 of Formula (5.2.11); SB-210661 of Formula (5.2.12); pyridinyl-substituted 2-cyanonaphthalene compound L-739,010; 2-cyanoquinoline compound L-746,530; indole and quinoline compounds MK-591, MK-886, and BAY x 1005;
- (b) Receptor antagonists for leukotrienes LTB₄, LTC₄, LTD₄, and LTE₄ selected from the group consisting of phenothiazin-3-one compound L-651,392; amidino

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compound CGS-25019c; benzoxazolamine compound ontazolast; benzenecarboximidamide compound BIIL 284/260; compounds zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195;

- (c) PDE4 inhibitors;
- (d) 5-Lipoxygenase (5-LO) inhibitors; and 5-lipoxygenase activating protein (FLAP) antagonists;
- (e) Dual inhibitors of 5-lipoxygenase (5-LO) and antagonists of platelet activating factor (PAF);
- (f) Leukotriene antagonists (LTRAs) of LTB₄, LTC₄, LTD₄, and LTE₄;
- (g) Antihistaminic H₁ receptor antagonists cetirizine, loratadine, desloratadine, fexofenadine, astemizole, azelastine, and chlorpheniramine;
- (h) Gastroprotective H₂ receptor antagonists;
- (i) α₁— and α₂—adrenoceptor agonist vasoconstrictor sympathomimetic agents administered orally or topically for decongestant use, selected from the group consisting of propylhexedrine, phenylephrine, phenylpropanolamine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, and ethylnorepinephrine hydrochloride;
- (j) one or more α₁— and α₂—adrenoceptor agonists as recited in (i) above in combination with one or more inhibitors of 5-lipoxygenase (5-LO) as recited in (a) above;
- (k) Anticholinergic agents ipratropium bromide; tiotropium bromide; oxitropium bromide; pirenzepine; and telenzepine;

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- (l) α_1 — to α_4 —adrenoceptor agonists selected from the group consisting of metaproterenol, isoproterenol, isoprenaline, albuterol, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol, and pirbuterol;
- (m) Theophylline and aminophylline;
- (n) Sodium cromoglycate;
- (o) Muscarinic receptor (M1, M2, and M3) antagonists;
- (p) COX-1 inhibitors (NSAIDs); and nitric oxide NSAIDs;
- (q) COX-2 selective inhibitor rofecoxib;
- (r) Insulin-like growth factor type I (IGF-1) mimetics;
- (s) Ciclesonide;
- (t) Inhaled glucocorticoids with reduced systemic side effects selected from the group consisting of prednisone, prednisolone, flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, and mometasone furoate;
- (u) Tryptase inhibitors;
- (v) Platelet activating factor (PAF) antagonists;
- (w) Monoclonal antibodies active against endogenous inflammatory entities;
- (x) IPL 576;
- (y) Anti-tumor necrosis factor (TNF α) agents selected from the group consisting of etanercept, infliximab, and D2E7;
- (z) DMARDs selected from the group consisting of leflunomide;
- (aa) TCR peptides;
- (bb) Interleukin converting enzyme (ICE) inhibitors;
- (cc) IMPDH inhibitors;

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- (dd) Adhesion molecule inhibitors including VLA-4 antagonists;
- (ee) Cathepsins;
- (ff) MAP kinase inhibitors;
- (gg) Glucose-6 phosphate dehydrogenase inhibitors;
- (hh) Kinin-B₁ - and B₂ -receptor antagonists;
- (ii) Gold in the form of an aurothio group in combination with hydrophilic groups;
- (jj) Immunosuppressive agents selected from the group consisting of cyclosporine, azathioprine, and methotrexate;
- (kk) Anti-gout agents selected from the group consisting of colchicine;
- (ll) Xanthine oxidase inhibitors selected from the group consisting of allopurinol;
- (mm) Uricosuric agents selected from the group consisting of probenecid, sulfinpyrazone, and benzbromarone;
- (nn) Antineoplastic agents that are antimitotic drugs selected from the group consisting of vinblastine and vincristine;
- (oo) Growth hormone secretagogues;
- (pp) Inhibitors of matrix metalloproteases (MMPs) that are selected from the group consisting of the stromelysins, the collagenases, the gelatinases, aggrecanase, collagenase-1 (MMP-1), collagenase-2 (MMP-8), collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), and stromelysin-3 (MMP-11);
- (qq) Transforming growth factor (TGF β);
- (rr) Platelet-derived growth factor (PDGF);
- (ss) Fibroblast growth factor selected from the group consisting of basic fibroblast growth factor (bFGF);
- (tt) Granulocyte macrophage colony stimulating factor (GM-CSF);

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- (uu) Capsaicin;
- (vv) Tachykinin NK₁ and NK₃ receptor antagonists selected from the group consisting of NKP-608C; SB-233412 (talnetant); and D-4418;
- (ww) Elastase inhibitors selected from the group consisting of UT-77 and ZD-0892;
and

Adenosine A2a receptor agonists.